this device be used to obliterate that shunt?

DR. HIJAZI: Dr. Hijazi again. Among the cohort of my patients I have four patients post-surgical closure of their ASD. One of them post-surgical closure twice with 13 mm residual ASD. We like. these cases because the margin is very stiff. You just go there, quick sizing, and the procedure is very successful. We had quite a few patients, at least in my personal experience, and I'm sure my other colleagues have encountered other patients.

DR. AZIZ: Also, if you had a patient who had a pacemaker, you would still be able to put this device in?

DR. HIJAZI: Yes. We have patients also that actually have pacemaker implantation, transvenous lines, that they had ASD that we go ahead and implant device closure. It does not really interfere with the packing lead.

DR. AZIZ: Thank you.

DR. TRACY: Thank you. I also enjoyed your presentation. I thought it was very good. I just had a couple of questions that I wanted to raise with you

and a comment. The first comment on the packet for the patient would take a Ph.D., I swear, it be able to read through that. I think the language is in much too sophisticated and you might ask Mr. Dacey for some advice on how to rearrange the language on that.

I believe the little angiogram that you showed of the fenestrated Fontan patient had a prosthetic valve in place so I would assume that patient would already be on Coumadin or would be transitioning back to Coumadin.

There is nothing in your labeling that indicates the contingencies for what to do with the patient who is on Coumadin. You do talk about anti-platelet but I would think that some language ought to be incorporated in that.

I also have the same question about re-ops but I think that has been answered satisfactorily. I think I will turn it over to Dr. Laskey.

DR. LASKEY: Thank you. The first thing I want to do is congratulate you for using a MacIntosh for your presentation. I appreciated that very much.

I came away from reading this with the

following conclusions. One is that if you are a young adult you'll do well with -- a young adult with an ASD you'll do well with this device. If you are a kid, child, you'll do well with surgery.

I know we beat the age issue up a bit. I do think it's important to dwell as an adult interventionalists I'm likely to see these people. How anxious am I do get involved with the nuances of "ASDs" in adults that are not really addressed in this study but which may comprise a significant fraction of the referral.

The first category there would be you have a fraction 7 or so percent who had bi-directional shunts. Can you tell me a little bit more about them? Did they have pulmonary hypertension or were they just so enormous that they were -- what set these apart from the pure left to right?

DR. HIJAZI: This is Ziyad Hijazi. These patients that had' bi-directional shunt they had a smaller ASD/PFO and sustained TIA or paradoxical embolism or dysrhythmia. When you do the contrast echo, often times in many of these patients there was

also right-to-left shunt.

DR. LASKEY: Do you think you have enough data here to support not necessarily efficacy but safety for this important subgroup of young adults -with PFOs?

Earlier on you said that the device would be used in people with PFOs but you didn't really address that in this study. I beg to differ that a PSO is not an ASD either physiologically or anatomically as you defined ASDs.

MR. LOCK: This is Ken Lock. It would be contraindicated in. the labeling that those patients would not be implanted.

DR. LASKEY: In what patient? In a PFO --

MR. LOCK: A PFO.

DR. LASKEY: -- with a cryptogenic stroke?

MR. LOCK: That's correct, a PFO patient.

DR. LASKEY: I see. Okay.

DR. WHITE: But were those included in this trial?

MR. LOCK: This is Ken Lock. There were three patients that did meet that criteria for the

study.

DR. LASKEY: Okay. I just have a few other questions. I don't want to steal Janet's thunder and I did have a few statistical questions.

DR. WITTES: You can do it.

DR. LASKEY: No. Just as a prelude. You do report 90 percent confidence intervals for one endpoint and then 95 percent intervals for another endpoint. Can you tell me why the choice of the one for the one and the other for the other and whether that might have made a difference for your lower 8 percent bound?

DR. LARNTZ : This is Kinley Larntz. The intention was to look -- when we use 95 percent bounds we were looking at a lower bound. I think that's what we tried to do consistently. You may find an example where we didn't do that.

When we report 90 percent they are two-sided so we are really concerned about the lower bound on that. It's really a 95 percent lower bound. In fact, I think we were consistent that we were using a 95 percent lower bound and doing that comparison.

I guess the answer is I think we were consistent and it wouldn't make a difference in the lower bound. We actually have, at least with respect to the protocol, a requirement. As was pointed out earlier, we met that with 5.2 percent as opposed to 8 percent which was a requirement.

DR. LASKEY: Thank you. I was just confused and I'll draw your attention to Table 8 in the beginning here, page 12 of the summary of safety and effectiveness data. It's expressed the one way there. Then on Table 27, page 35, in the Panel Pack it's expressed. It's just a little confusing. Then FYI you have a lower bound of -1.052. I'm sure that's a typo. You mean -0.052.

DR. LARNTZ: It's 0.052. I apologize. I saw that typo earlier.

DR. LASKEY: I just wanted to be sure of that.

DR. LARNTZ: I wondered also about the dependence of efficacy of, well, the outcome on size of ASD. While there appears to be no relationship with primary efficacy at 12 months, there does to my

eye look like a fall off in the composite endpoint at 12 months with size.

Is there any -- am I missing something here? Is it more difficult to treat these the larger they get? Your numbers do trend down as you go from 6 mm to the 38 mm for the composite endpoint but not for your primary efficacy endpoint at a year.

MR. LOCK: This is Ken Lock. We did notice a trend in the composite analysis. One of the failures for the composite analysis, as we have stated in the presentation, was that the patients weren't allowed to revert to a success so we have more failures, I guess, reported in that.

You are prepped in the primary efficacy that in the end they will become a success. I think I'll have Dr. Hijazi answer the question, "Are larger defects harder to close?" I think he will be able to answer that for us.

DR. HIJAZI: This is Ziyad Hijazi. In terms of the larger defects, Dr. Laskey, there's no question that they seem to pose slightly more challenge to the operator than the small 10 mm straightforward ASD.

However, that's why experience, I think, is important when you train people about larger defects.

They do seem to pose a little more challenge but at the end if you look at the results, and we looked at that in terms of the learning curve and everything. There was not really much of a difference between the people who did 10 ASDs or 50 ASDs.

DR. LASKEY: In that vein are you likely to be older if you have a larger ASD or did this not -- I know to the best of your ability you couldn't find a relationship with age here. My brief experience with young college students who come through an adult congenital clinic is that these are gigantic defects usually.

DR. HIJAZI: I agree with you. I think, you know, the older you are the more like that the patient will have a larger ASD. We know that this continued left-to-right shunt through the years does result in a larger ASD as they grow older in age. There's no question when you look at our adult patients they tend to have. larger ASDs. I don't know why they were missed all these years.

DR. LASKEY: But they are. Hence, that brings us back to what we're trying not to badger you with but there is an age issue here which is related to the entity itself which it's difficult to make comparisons with the surgical data.

DR. HIJAZI: However, as I mentioned in my presentation, Dr. Laskey, that the mean ASD size for both groups were compatible. 13.3 mm for the device and 14.3 mm for the surgical group. And the same percentage of patients in both groups had significantly large right ventricle. Although they were different in ages, but what we are treating, the ASD itself, they were similar in that aspect.

DR. LARNTZ : If I might follow up just slightly on this. This is Kinley Larntz. It is true that the average age differed, but it is also true that there is a wide range of ages in both groups. In fact, the table you pointed out to me on page 49 indicates the quartile distribution of ages.

Just for reference, if I can, and this again is partly from memory but I think my memory is pretty good on this, the lower quartile is less than about

3.7 or four years. In fact, there were 76 patients in the device group that were less than that.

The second quartile is somewhere -- well, it's obviously greater than whatever I just said, 3.7, up to about six years. There were 102 patients in the device group in that cohort.

Then the next quartile runs from the six up to -- again, it's from memory. I apologize for not looking it up and bringing my notes -- about 18 years. The mean ages, of course -- this is statistics, right? -- heavily influenced by some much older patients that skews the mean. The medians are quite a bit smaller in both groups.

DR. LASKEY: That was my next question. If it's non-Gaussian, then it's not fair to compare the ASD's sizes as means but you need to do it as medians, too. Is the median ASD size in the surgical group larger or smaller than the median ASD in the device group?

DR. LARNTZ: This is Kinley Larntz. I don't know the answer to that.

DR. LASKEY: I would bet they are not the

same but it's easy to do.

DR. LARNTZ: It's easy to. I agree.

DR. LASKEY: Thank you.

DR. TRACY: Dr. McDaniel.

DR. McDANIEL: Thank you. I have a few comments on some of the grammar or terminology on some of these things. Maybe suggestions for the contraindication to the device placement where you state, "Any patient with the margins of the defect less than 5 mm to the coronary sinus AV valves and right upper pulmonary vein." Should that be or? I know this is picayune but if you leave it as "and" you're kind of raising your standard as to your contraindication. It's picayune, I admit.

The next question on this, and this is also in the same portion of this information where on page 4 -- don't ask me which section I'm on here -- on alternative practices or procedures. You probably should mention that there is an alternative of doing nothing as opposed to just device closure surgery. Kind of standard medical care is that you always have the option to do nothing, or the patient has that

option.

I guess now getting into the patient packet of information, I'm not sure it requires a Ph.D. I have read over this and had a couple of questions on it. One is under the first paragraph of introduction with an ASD. It says usually the hole is in the upper part of the atria1 septum. Most pediatric cardiologists would say secundum ASDs are in the mid portion of the atria1 septum.

I think, again, that's a minor point but to families reading the literature, or somebody else looking at this you might think sinus stenosis and that's not at all what you're talking about.

Then on page 10 of 23 on the patient information, the second to last paragraph, "Because it is receiving so much extra blood, the left side of the heart does more than its share of work." It's the right side of a heart in an ASD.

Also the sentence says, "Plus the blood is poorly oxygenated." Well, actually, the blood on the right side of the heart is more oxygenated than normal so this is a physiologic error there.

I guess also on the patient information you have four figures which you've used elsewhere from the transesophageal echo, the cartoons. I think that the fourth figure, which is listed here as figure 7 on page 14 of 23, but it's also earlier in your packet, looks very different.

I understand what you're showing, that once the device is released you no longer have retraction of the atria1 septum so it moves. Particularly to a non-medical person looking at this picture, it looks very different so I think they might find it confusing because before you've shown part of the tricuspid valve and now you have this other -- you're not showing it in the same way.

I just think it's potentially confusing to the families what you were illustrating. Also, on the patient information as a pediatric cardiologist the patient's parents are confused by this all the time. We're now on page 15 of 23 of the patient information, second sentence, where it says something about an adhesive bandage where an incision was made to insert the catheter.

Patients think incisions have like sutures and those sorts of things. Generally none of these procedures are done with incisions truly. I think it would just be confusing to the families or to the patients themselves if they're adults.

Pardon me. I'm going to look through all my little red stickies here. Looking through the extensive list of individual patient data and those sorts of things, there are a fair number of misspelled drugs and stuff. It doesn't matter but I actually did read it. I wanted to point that out.

I have two additional comments. One is to echo the concerns that surgical practice has changed very much in the last 10 years, particularly related to ASD closure with limited incisions, very short times in the OR.

I can't find the table in here but the length of procedure which you compare the device versus surgery, there was an incredible outlier in the surgical data. Over 300 minutes for an ASD closure for procedure time. That would be very unusual. I just wanted to point out that one patient alone may

skew the data a bit.

Then, again, point out that with -- I understand about no literature being out there as far as what is an acceptable fenestration leak in the fenestrated Fontans but, again, I would point out that going from an average of 4.7 mm hole to a 2 mm hole may be successful but its' not the same as enclosure of the ASD.

My second comment on the fenestration is that in one of the tables you referred to secondary fenestrations. My question is are those really baffle leaks that you're closing and is that an important distinction?

MR. LOCK: This is Ken Lock. I'll have Dr. Moore address this question.

MR. MOORE: John Moore. The secondary fenestrations, as far as we know, could have been baffle leaks. As opposed to being intentionally placed punches they probably were baffle leaks.

DR. McDANIEL: That's all.

DR. TRACY: Dr. Wittes.

DR. WITTES: Hi. I'm Janet Wittes. I

apologize for being late. It's very hard to get back from Bangor, Maine, on a Monday morning.

I'm a statistician at Statistics Collaborative and I'm a regular member of the panel. I deal with denominators a lot. You're going to have to bear with me about some denominator things and the age.

I also am very worried about the age distribution. Can we start with it? Because I would like to start on tab 1.0, the yellow tab, page 6, where we have the raw data. That, to me, is what really tells us where the people are.

Whatyou'llnotice -- maybe you've discussed this in detail before but I'm concerned about statistical adjustment when there's no people in the categories that you're adjusting. If I could just compare children to, say, goldfish and I can adjust them and get an answer.

I'm nervous about comparing two different distributions where there's a blank in a big part of the age distribution. Yes, there's people in all the quartiles but there are people in all the quartiles by

definition. There's always going to be people in four quartiles. There's nobody in the surgical group above 40. There's only one person above 30. There's only five people above 20.

It seems to me that the correct analysis -- I mean, again, we recognize this isn't randomized but, nonetheless, it seems to me the only analysis one can make is an analysis that is limited to the 30 years where you don't have a denominator -- or 20 years where you don't have denominators in the surgical group of effectively zero.

So my question is if you look at the data limited to where there are people in both age groups, how would that affect the comparison of your primary efficacy?

The other question is where did the failures occur?

DR. LARNTZ: We have five failures.

DR. WITTES: Yes. Where did they occur?

DR. LARNTZ: I don't know the exact ages of those. This is Kinley Larntz, by the way. We can determine that but I don't have the ages of those

patients in front of me.

DR. WITTES: I would like to know because to me it's very different if they occur in the older group where there's no surgical people or in the younger group where you actually have some.

MR. LOCK: This is Ken Lock. It will take me a couple minutes but I will get that for you.

DR. WITTES: Okay. Great.

Question No. 2 has to do with, again, denominators and follow-up. It's actually -- it's going to be a kind of multi-tiered question because it relates also to the difference between the primary efficacy and the composite efficacy and to the question about an apparent decrease in efficacy as the lesion gets bigger. It's one question but intertwined.

It starts really with a question about -- the other piece that's related to is the difference between retrospective identification and prospective. My understanding is there's basically 440 -- well, there's 400 and something or other that started and there's 331 with primary efficacy data. What you say

in the text, I think there are 68 who missed their 12-month follow-up and eight more were lost at follow-up.

That's basically 25 percent of the population -- the group. Assure me that there aren't hidden failures in here.

MR. LOCK: This is Ken Lock.

Jodi, if you could put up bar backup slide No. 7, please.

I apologize for the darkness of the slide. We looked at these -- took these very seriously these missed visits. We have extensively worked with the investigators to try to find out exactly what the status of these patients are.

Since the filing of the PMA 28 of those patients have come in for a visit. The shunt status is up there, 27 were closed and one had a small shunt of those 28 leaving 40 patients'left to look at. Five patients were seen and data was not available on those patients. We are still collecting that information.

There was the one death that was reported in the PMA that was after the one-year visit but is no longer available for follow-up. Five patients are

scheduled now here in the next six weeks. It really leaves 29 patients left out of that 68 that we are still trying to attempt to locate. However, they are not responding to the letters and phone calls.

DR. WITTES: Okay. The worry always is that people who are hard to follow are different from the others. Either they are in such great shape that they just don't want to be bothered', or something bad has happened. Given that you're talking about very small marginal differences between the two groups, I think it's important to find out.

DR. HIJAZI: This is Ziyad Hijazi. On those 29 that have missed their 12-month follow-up, we went back to see when was the last time they were seen, the six month follow-up. Their six-month status is shown there. Twenty-eight of them had complete closure.

Actually, this one that says moderate shunt, Dr. Moore just informed us last night that he saw that patient just last week and he has completely closed the defect. Out of the 29 had complete closure. This is based on their six-month follow-up. We are working aggressively to get the follow-up on all these

patients.

DR. WITTES: Okay. The amusing thing, of course, is that by definition with the surgical group you have full follow-up because it's retrospective. Well, basically.

DR. HIJAZI: No, because only 37 patients were retrospective and addressed to the surgical patients who are perspective.

DR. WITTES: So how come you had such good follow-up?

DR. LARNTZ: This is Kinley Larntz. I guess I'll plead guilty to being a little inconsistent. Okay? That's not unusual for me. I'm a statistician and we should all be perfectly consistent. Here is what we did. The surgery group is actually quite hard to follow. That's actually true.

DR. WITTES: That's what I would assume.

DR. LARNTZ: The surgery was quite hard to follow. A decision was made that we would carry forward the surgery results to the 12-month follow-up. Okay? In fact, when it looks like we've got great fault, that's a carry-forward analysis for the

surgery.

Once closed we assumed, and I've been assured that surgeons once they think they're closed, they're closed. That was an assumption. It.was taken as a worse-case scenario that, in fact, if the surgery group had all closure. We weren't quite consistent. I said that.

If we did the same carry-forward analysis that Dr. Hijazi just mentioned we could do because we did have six-month data on a lot of patients, if we did that we would uncover a total of -- there would be five more cases of non-closure at earlier periods.

There were five failures at 12 months and there would be five more which if we were redoing the calculations with that as a carry-forward -analysis, which we could do and we did do, we would find that the lower bound that we needed for efficacy, instead of being 5.2 present, it would go to 5.9 percent.

DR. WITTES: But you know I would really fuss at that.

DR. LARNTZ : We didn't put that in the report but we did the calculations just in case

someone wanted to bring up the issue. It is an inconsistency. We could have done a carry-forward analysis and I myself would have had some difficulties. I'm not sure I love carry-forward analysis.

In fact, I know I don't love them. Given that we do have information, if you make the same assumption for the device group as the surgery group, we could, in fact, evaluate all the patients and we would wind up with 10 failures out of the whole group. I'll stop at that point.

DR. WITTES: Then again I think one of the things that this is just emphasizing is how different these two groups are. They are different in many ways by the very nature of the way the data are collected.

Okay. Well, given that and the denominators and given the problem with ages and sizes, can we go to yellow section 1.0, page 40. I read these also in a way that sort of says if I look at the 12-month composite endpoint, I'm seeing a decrease in efficacy as device size and, hence, the legion size is getting bigger.

But if I look only at the primary efficacy, I think the naive reading is it stays the same. But if you look a little closer, it seems to me what it's saying, and this is where I need help, is that the denominators have changed so that while the 12-month composite keeps everybody in the denominator.

The primary efficacy looses people. For example, let's go to the 13 mm. Here we've got 15 in the numerator in both the 12-month composite and the primary efficacy, but we have an extra person in the denominator in the 12-month composite.

It seems to me what's happening is that the 12-month composite is keeping as many people as possible and you're seeing that as the device gets bigger, the failure rate gets bigger. The primary efficacy by the way it's defined is losing people in the denominator so that the numerator and the denominator stay the same and you get 100 percent.

Now, what I'm asking is, the question I'm trying to get at is the following. Which is real? All right? Is the decrease in efficacy that we're seeing as a function of size in the composite, is that

real? Or is the constancy that we're seeing in the primary efficacy, is that real? It's clear why this is an important question to address.

DR. LARNTZ: This is Kinley Larntz. There's the main aspect of the composite. First of all, the composite, I think, we calculated it assuming that a shunt at anytime was a failure. The agency this morning in their presentation said that we had misunderstood. I apologize for that. And that we should only count shunts at 12 months as failures.

There were some procedural shunts that would not be counted as failures if we redefine the endpoint. Those procedural shunts turn out to be related to size. That is, larger ASDs tended to have procedural -- tended to have shunts right after the procedure that were larger than the smaller ASDs. That's part of it.

The second part, and the reason you've got denominator changing partly is that technical failures; that is, failures to place the device were included as failures in the composite, technical failures. The primary endpoint was as a denominator

the number of devices that were placed.

DR. WITTES: Okay. So the reading is that it's more difficult to place larger devices?

DR. LARNTZ: There's clearly an effect. That's clearly a statistical effect that larger devices, the technical success rate decreases slightly. It's not a lot but it decreases slightly and that is associated with size. I think the physicians could probably talk about things related to how close you get to the -- how much rim you need and things like that for larger defects.

I don't deny and, in fact, I admit there's a statistical effect that larger defects tend to have lower rates of technical success related to, I think, anatomical conditions related to larger defects.

DR. WHITE: Did you not count some of those failures as just bringing somebody to the cath lab and not yet having a large device available? Weren't they also counted as failures?

DR. LARNTZ: Yes.

DR. WHITE: Is that what you said in here?

DR. LARNTZ: Yes.

DR. WHITE: And then some of those people came back later and got the device when a larger one was available, would they have been counted as composite failures?

MR. LOCK: This is Ken Lock. The intent to treat patients where a device was not placed or even introduced to the body were not included in the composite. However, like you say, a couple of patients came back and had successful procedures.

DR. WHITE: What I'm saying is you would buy us your data against larger devices. If I thought it was a 30 mm device and I had one to close but I got in there and I found out that the balloon actually said 34 so I don't have a big enough device yet, did you count that as a failure or no?

MR. LOCK: We counted that as an intent-to-treat, not as a failure.

DR. WHITE: Not as a failure. So then that wouldn't go to your question of why the bigger ones fail more often.

DR. WITTES: Okay. Then I think I have one more question and then a comment. This actually

relates to a question that was brought up earlier that some of the -- I mean, there are not many failures and they went on to surgery. If there were five failures, there couldn't have been more than five of them, right?

DR. LARNTZ: There were five.

DR. WI'TTES: All five them --

DR. LARNTZ: No. I'm sorry. What happened to those failures?

DR. WITTES: Yeah.

DR. LARNTZ: Oh.

MR. LOCK: Maybe we misunderstood that. There were five failures but none of them have gone on to have their defect closed.

DR. WITTES: Oh, then I misunderstood that. I thought you said -- okay. So they did not go on to surgery so none of the surgery people were people who had been device failures?

MR. LOCK: Correct.

DR. WITTES: I'm sorry. I misunderstood. Okay. My final thing is actually a comment and it has to do with the patient brochure which I thought was

really nice. With some corrections it would -- I thought it was -- I really thought that what you were doing was trying to convey to patients and their parents the physiology and what this device was and I thought it was very, very nice and I hope that you will in making the changes, not eliminate the general feeling about it.

DR. TRACY: Dr. Crittenden.

DR. CRITTENDEN: I just' have a couple questions and a comment as well. Could someone tell me how many patients need a general versus local anesthesia? Did you have that broken down? Is that something that is fairly common for general anesthesia to be used?

MR. LOCK: This is Ken Lock. In the device group all patients received general because of the use of the TEE.

DR. CRITTENDEN: Okay. Dr. Hijazi, could you discuss your experience with multiple device deployment? That seems to be a little bit more problematic. Could-you talk about that a little bit, please?

DR. HIJAZI: Sure. This is Ziyad Hijazi. Multiple defects are present in patients with secundum atria1 septal defect, either a second hole or multiple holes. What our, at least my, policy is and the policy of my colleagues is if the holes could be covered with one device, we would use one device to cover everything. That is usually true in the fenestrated type of atria1 septum. We have quite a number of these patients in this study.

If the hole is far away from the primary hole, it may require a second device simultaneously. I have actually done over 10 patients myself with two devices simultaneously. We published the paper that came out two years ago describing 22 patients who received two devices.

Their procedural time, fluoroscopy time, success rate and everything is similar to those patients who have a single device. Yet, it is more challenging but I think because of the versatility of the device, it allows you to do these things with great safety.

DR. CRITTENDEN: The next question is does

anybody really know what the natural history is of these residual shunts given that there may be more failures of residual shunts given that there may be more failures of residual shunts -- I should say not failures in the larger sizes.

We put more patients at risk for cryptogenic stroke, paradoxical emboli that we're going to create a disease with this? Not create but you understand. We're going to put more people at risk for this.

DR. HIJAZI: Ziyad Hijazi again. Very good question. The natural history has been published in many manuscripts after device closure that the majority of these tiny residual holes that are left in a patient, most of them they go spontaneous closure down the road.

Now, I do not know of manuscripts or reports that came out of patients who have small residual shunt. A few years down the road some of them have the TIA or something like that but I think that is an important question.

DR. CRITTENDEN: Finally, a comment. I was here in 1997 as well and remember it was quite a

contentious panel meeting vis-a-vis what kind of comparisons could be made between device closure and surgical closure.

I guess this part of respect represents my bias as a surgeon that I think we could have done better. I'm really disappointed that we didn't have a better study that could have been done in the past four years. Mentally I understand that more patients are going to opt for having a device versus surgery.

I mean, that's common sensical but I think we could have worked with surgeons in a more formal way. There's really an unfair comparison and we're basing a lot of conclusions on the comparison I think is highly flawed. That's all I have.

DR. TRACY: Are there any other questions going around again through the panel members? Dr. Williams.

DR. WILLIAMS: Just one follow-up question. I think on page 55 there was a difference in the secondary effectiveness variable among the sites.

I would like to just ask Dr. Hijazi if he has any wisdom about the learning curve for an

institution or the operator or the secondary people such as the echocardiography that would advise us in terms of conditions once this device is available more widely that should be included as a condition.

DR. HIJAZI: Yes. This is Ziyad Hijazi. I will answer part of the question and leave the rest to Mr. Ken Lock about the training guidelines that we have.

There is no question that anything in you that you do has a learning curve. There's no question that anything new that you do has a learning curve. I do believe that with such an ideal device like the Amplatzer Septal Occluder with the ability to recapture, reposition the device gives the individual the ability to perform the procedure much better.

Obviously the individual has to be a very good interventional cardiologist but the interventional cardiologist is not the only person involved, although the person is doing the procedure.

Echocardiology is extremely important guiding the entire procedure so collaboration between echocardiography and interventional cardiology will

result in the least minimal amount of learning curve for that institution.

The other good news is that now most cardiac centers across the country are involved in one or more of the other devices that are undergoing clinical investigation. There's no question that the Amplatzer Septal Occluder has the least difficulty for a person to learn how to implant the device.

Let me put it like that. I think we will do very well with the training of the new physicians who are using current devices once the device gets approved. I'll leave the rest for Mr. Lock to talk about the other guidelines.

MR. LOCK: First of all, I wanted to speak regarding the one site that had a lower success rate. Again, keep in mind that the composite success kept those shunts and that did not reverse to success. That particular center had six procedure failures meaning there was a significant shunt post-procedure.

Then eventually those patients all were successes at 24 hours or six months. That's the first part to the question. What I have up on the screen

right now is a training program that we would like to implement at AGA.

This would be really three parts to it. It would be the tiered release of the device. Once we would have investigator approval to go ahead and implant, the Tier I would be our current investigators who have experience with the Amplatzer technology.

Then the second tier would be interventional cardiologists withexperience with othertranscatheter closure devices. The third tier would be just interventional cardiologists that we would proctor and train.

We would also require hospital approval and the hospital will be approved if the following are met. That they have surgical backup and that they have access to transesophageal echocardiography.

And the last slide here talks about the proctoring. We will assign proctors who are experienced clinical investigators and once a site is identified and approved as a site, the proctor will assist in the first three to five cases. We would like the proctor to after three cases assess how the

new investigator is doing and then assess if there's more need for the proctoring.

Also the proctors will act as regional technical support so if there are any questions, they can be called upon to assist as needed.

DR. TRACY: Can I just ask what you mean by surgical backup? Does that mean an OR open on standby or what precisely are you asking for?

DR. HIJAZI: Ziyad Hijazi. Surgical backup would mean the presence of a surgeon in the hospital without the need for an open OR at the time. Even the five patients that we had embolization in them, patients were totally asymptomatic from hemodynamic point of view.

As a matter of fact, one of them had embolization over night and was ready to leave the hospital. Of course, we do echocardiogram and chest x-ray prior to their departure and we found the device embolized. We do not require like angioplasty or stent. Even now with angioplasty and stent they change it. Just in the house.

DR. TRACY: Dr. White.

DR. WHITE: I don't want to drag this out but I wanted to ask a couple of specific things. You have not in your exclusions eliminated patients with severe contrast 'allergies. Is that your intent? Do you not want to warn the operator that if a patient has a known severe contrast allergy, that they should not undergo this procedure?

MR. LOCK: This is Ken Lock. I think that we would include that as a contraindication.

DR. WHITE: And regarding your training of physicians on the section 3A on page 2, I guess --

DR. HIJAZI: Dr. White, your point about the severe contrast allergy, I personally as a physician would implant the device in a patient with allergy doing it without angiography with TEE and fluoroscopy without injecting dye so I don't think that it should be added as a contraindication for device implantation.

DR. WHITE: To contrast. Right.

DR. HIJAZI: Yes.

DR. WHITE: I think you need to handle that just on the labeling issues for the physician who

needs to understand that you at least don't think that's a great idea to do that so that he pays attention to that as a plus or minus.

Under 4-l you talk about the septal occluder system should be only used by those physicians trained in transcatheter defect techniques. My question is do you not want to say trained in the Amplatzer device or are you suggesting that if someone has skilled with any device? Is that what you mean? You mean generically or specifically?

MR. LOCK: I think generically. As I said, in the Tier II those will be our second round of investigators that would be trained in the Amplatzer technology. Our feelings on that were that if they have experience with septal occluders, in general they would understand the concept.

DR. WHITE: So the difference between the devices is not enough? I mean, they are pretty close to being there with a smaller amount of education than somebody who has not done this at all?

MR. LOCK: That's correct.

DR. WHITE: Under 4.2 you mentioned on your

slide about backup surgery. I think that I agree with your caveat but I think it ought to also be spelled out that you believe that onsite surgical backup ought to be available. I don't think you need to have an open OR but you don't want to have this procedure being done in places that do not have surgery onsite. I think that's an issue.

Under B under Patient Labeling under Observed Risks you have listed the marker band embolization which is no longer an issue. You should probably delete that since marker bands are on the device. Under Potential Complications under Patient Labeling should you not list the left ventricular heart failure, the decompensation that potentially. could occur?

I mean, is it possible that someone could have left ventricular heart failure with closure of this device? Is that a potential complication? You may not have intended it or may not think it's likely but it is a possibility.

DR. HIJAZI: Yes. This Ziyad Hijazi. This is a potential complication and usually in older

patients with a stiff left ventricle if you close it.

DR. WHITE: So that ought to be listed for the patient.

Then finally under Appendix B -- I'm sorry, Appendix A at the very end you've listed that your device is tighter and more secure. It says, "The Amplatzer Septal Occluder is relatively new. How do we know it is going to be reliable?" You say its design allows a tighter more secure seal than provided by other devices.

Do you have any evidence for that comparison? If a patient reads this, are they going to pick your device? You want a patient to pick your device over a competitor's device based upon this?

DR. HIJAZI: Ziyad Hijazi. We'll take this out, this comparison, from the note.

DR. TRACY: Dr. Laskey.

DR. LASKEY: I just have a quick question for Dr. Wood. Is there ever a circumstance where you need to close the fenestrations surgically? In other words, mandatory?

MR. MOORE: This is John Moore.

DR. LASKEY: Sorry.

MR. MOORE: The protocol certainly did not require any specific setting to direct the patient to surgery as opposed to device closure. If the patient was going to require surgery anyway for prosthetic valve replacement or whatever, then transcatheter device closure is unnecessary and would not be suggested.

DR. McDANIEL: McDaniel. I'll ask another question along those lines. If the secondary fenestration or baffle leak is very close to the pulmonary artery and anastomosis, do you have any data suggesting the Amplatzer can be put in that position or is that someone you would send to surgery?

MR. MOORE: Well, there is a suggested rim requirement of 5 mm in general as has been alluded to by others. These are small devices and a 5 mm rim essentially is plenty.

DR. TRACY: Do any of the other panel members have any questions?

Dr. Wittes.

DR. WITTES: Yeah. I wonder whether you

have the data yet.

DR. LARNTZ: I have not been able to get that. I will get that shortly. It will just take me a minute.

DR. TRACY: Two more in that direction.

DR. ZAHKA: Do you have any sense what the recommended age or weight will be for this procedure assuming that standard practice. for atria1 septal defect surgery is X? What will this be?

DR. HIJAZI: This is Ziyad Hijazi again. I think we will adopt the same criteria and indications similar to the open heart surgery. In every textbook of cardiac surgery when you read in papers they say that usually it is done before the child goes to school.

So if you have a one-year-old child with ASD, personally I would not send that patient to surgery even if devices are not available at all because that's not the age when we send patients to the OR.

We usually send them three to five years of age. I would do the same thing for devices. My

recommendation for children is to undergo the closure just prior to them going to kindergarten.

DR. ZAHKA: Then I have a question about the geometry of the defect. Let's say that a defect is very oval in shape.

DR. HIJAZI: Yes.

DR. ZAHKA: The surgeons obviously change the geometry of the defect dramatically when they take a round defect and make it a slit and close it off. You are, in fact, doing the opposite if you took an oval or slit defect, you make it round and you stent it open. Do you have any sense that there is a subgroup of patients that have more arrhythmias or more this or more that as a result of stenting a defect open that is not circular?

DR. HIJAZI: That is a good question. Ziyad Hijazi. We do not have data on patients who have oval defects whether they had more complications or not. The complication rate of arrthymias in general is low in this cohort of patients. I think follow-up of these patients we'll find out whether changing geometry of the atria1 septum will cause a problem or

not.

My gut feeling tells me that most likely we will not encounter the problems,--that these patients are encountering after open-heart surgery on the long run with atria1 ar-rhymias.

DR. ZAHKA: My last question is do you have a sense of what the timeline will be between Tier I, Tier II, and Tier III rollout for training of physicians?

MR. LOCK: This is Ken Lock. If it's approved today and as soon as the device is available, whatever that time frame, we haven't really looked at what the time frame is we will need to roll it out to those sites.

We will be very careful to make sure that we would take our time to get out to the Tier III. So really the Tier II will be the first ones that will be trained in on it over the next few months and then we will be cautious to move forward to the Tier III.

DR. TRACY: Dr. Hopkins.

DR. HOPKINS: I'm glad the training -- I didn't really focus on that the first time around so

I'm glad it's come up because I think that's very important in these kinds of devices.

Is it your intent -- and given what Ziyad was talking about in terms of the experience with the larger defects and, with all due respect, not everybody is as talented in the cath lab as Dr. Hijazi. Is it your intent for the Tier III interventionalists that they would also be approved to attack defects larger 'than 25 mm?

Would there be any commendation at least by eyeball as the other panelists and as you yourself had indicated pose a greater level of difficulty which it appears the break point is around 25 mm that maybe those should be centralized and not fully opened to the total market? What is your intent?

MR. LOCK: I guess in those particularly cases where there are large defects have the size available because when you go into the lab you don't really know until you stretch size the device -- the defect. I'm sorry. We would be willing in those cases where we think that might be a larger defect have proctoring available and technical services

available.

DR. HOPKINS: But your intent is in the Tier III that they would have equal access to the larger sizes?

MR. LOCK: Yes.

DR. HOPKINS: Just to comment again, I think I understand exactly what you said about the recommendation for closure. It does go back to the study design. I think all of us feel that ASD should be closed between the age of 3 and 6 and we not even deal with these older patients ever again. The study that is supporting the device is one done in older patients, not effectively to the kinds of numbers in the total device in the younger patient. That's just a comment, not a question.

The one final comment I would ask you to look at is in the patient literature that you give the patient. I would also agree that I thought it was a very good patient manual. Right above where it says, "Alternatives to device and treatment," you talk about the benefits of the procedure. This is on page 20 of 23 where you say many patients have the procedure done

in the morning and go home at the end of the day or the following morning.

I would ask that you look seriously at the next sentence which says, "You won't have to endure the lengthy recovery period that would be required after surgery." I think that is a little loaded. Most of our patients go home the next day as well. It just seems a little strong in its language. I don't think you lose much by deleting it.

DR. TRACY: Any other questions from the panel?

Mr. Dacey.

MR. DACEY:' I would like to address the patient information. All too often we make some assumptions about our patient populations. The rule of thumb as been for readability 5th grade level. That's been a national criteria. As I look through this, a few things occurred to me.

Clearly there are level and informed consent requirements in preparing patient information/ education literature. There is also this daunting task for physicians that you have this full spectrum.

It's wonderful to say, "YOU should talk to your physician about any questions or concerns you have."

That's correct but the community I live in the parent of a child with an ASD, one parent might be an astrophysicist whose been on the website and gathered volumes of information and come into the doctor's office with that and book in three hours of time to talk -about it.

Of course, at the other end is the family who may not even speak English and they've got this information put in front of them and they can't even read it. Then I get into it and I look and I see medical jargon and I see illustrations like Figure 1, normal heart blood flow.

Then the next one is generally the same information but it's really a different illustration. It's those little tricks that confuse people. Then when you get into language, I looked at this and it says belly and legs. Now, that's 5th grade level. The higher level, of course, would be abdomen. It cries out to be simplified.

As I further went on -- well, I'll skip that

one. The illustrations, the vein access sites are generally good but I would want to make them larger because there's an assumption that people can ready small things. That's not true.

Then you get into this jargonese, "The occluder is compressed into the catheter for delivery." Where are you going to deliver it to? This is a language issue.

Then we get over to Figures 4, 5, 6, 7. The previous illustrations are line illustration and all of a sudden we're looking at diagrams made off of an echo and there's no'relationship back and forth. This will further confuse people.

There is really some very good patient communication expertise out there. If I can digress just for a moment, I've put a lot of time in the patient education area and communication with some ASD patients and families.

It turns out that the most remarkable teaching tool has been the model of a heart that the physician can use to point out exactly what's going on, where, and what they are going to do which is

complimented by the printed material.

I understand that deals with the practice and not the efficacy and safety but I'm always concerned that patients get the information they need to make the best decision possible which is what everybody here wants also. I guess that summarizes my comments. Yeah, that's it.

DR. TRACY: Thank you.

Mr. Morton, questions'or comments?

The sponsor looks like they have one more comment.

DR. LARNTZ : I just wanted to answer the question about age. The ages of the five failures, 3.6, 4.1, 5.2, 10.3. 15.9.

DR. WITTES: Can I do some calculations?

DR. LARNTZ: Sure.

DR. TRACY: Dr. McDaniel.

DR. McDANIEL: While she makes her calculations, one final comment on patient education material. You make the suggestion or statement that animal studies and clinical studies where thousands of patients have proven this reliability. Maybe there

are thousands but, you know, it may be an overstatement. I don't know if it needs to be in there.

DR. TRACY: Dr. Crittenden.

DR. CRITTENDEN: I have a question that I'll ask while we're waiting for the electronic abacus to work here.

Dr. Hijazi, how many of the 4 mm and 38 mm devices have you deployed?. Do you recall off hand?

DR. HIJAZI: I do not recall the exact number but I can tell you I have put a large number of the larger devices including the 40 mm, which is not being sought for approval here, obviously outside the United States.

Fifty percent of my patients in Chicago are people with very large ASDs about the size of 20 mm. About 45 patients with devices 28 mm to 40 mm. With the smaller most of my Fontan patients are the smaller devices, 4 or 5 mm. I'm sure Dr. Moore the same thing with his Fontan patients.

DR. CRITTENDEN: So for indications for ASD you thionk you need all those sizes?

DR. HIJAZI: Yes. Definitely.

DR. CRITTENDEN: As opposed to Fontan. IN the Fontan obviously you need a smaller one.

DR. HIJAZI: The smaller sizes for the Fontan and the small ASDs. Adult patients with their large ASDs you need the large devices to close their defects.

DR. CRITTENDEN: Thank you.

DR. TRACY: Dr. Wittes, have you finished your calculations?

DR. WITTES: Yes. I can't do any calculations but I'll tell you what my concern is. Now, if the criterion for success is this prespecified 8 percent, what this is saying is that all the failures are occurring in the young age groups where you actually do have surgical controls.

What I worry about is if you look at the data on page 6, it seems to me what it's saying is you have a comparison between kids less than 20 in the two groups. You don't have a real comparison over 20.

You say that the five failures are all occurring in that less than 20 group. You are

inflating that denominator in the device group by those people where there were no surgeries.

If you were to have made the direct comparison in the age group where you actually had data, I don't you'd hit your criterion. I was trying to calculate but I can't and I don't want to give the wrong number. The point is it seems to me this bears on the message that's coming out is you're almost -- you're equivalent.

You're not inferior if you use the devise. Yet, it seems to me that's an artifact, at least in part, of a very peculiar age distribution where there's no older people in the surgery group. I don't know if I made myself clear.

DR. TRACY: Can I just -- no. I'm confused because isn't it possible in some way just to lop off the older patients and just do a comparison between the Amplatzers versus the surgicals up to the age at which --

DR. WITTES: That's what I was trying to do but my machine didn'twant to give me an exact answer.

DR. TRACY: Do you have any information that

would answer that question?

DR. LARNTZ : My information is that it's going to be -- with respect to that group if you chose under 20, which I've not done the calculation, but I'm willing to speculate and my speculation is that it will be close to the boundary.

I don't think it's going to be going much below 8 percent because it's at 5.2 and, by my calculation, about 75 percent of the patients in the device group are under age 20 if I just did a rough calculation.

By that we will decrease the denominator by the same number of events. I think it will go down obviously. It will get very close to the 80 percent but I cannot give you an exact number right now. We could do that at some time but it's going to be very close.

DR. TRACY: Dr. Williams.

DR. WILLIAMS: I think if we were going to through the process of recalculating things, we ought to make sure that we retain the most important issues for the patient and remember that there was very

conservative accounting for in terms of both -- in terms of efficacy.

I would say that if we were going to truly compare the same age ranges, I wouldn't be concerned about those who had shunts that closed before 12 months because I don't think that's important.

Just remember that there was a lot of very conservative calculation in favor of the surgical arm when this was done. If we evened that all out, I also have the impression not being a statistician that it would come out at least very close, if not still on the favorable side.

DR. TRACY: Okay. Any additional questions? If not, I'll ask the sponsor to step back from the table and we will review the questions posed to us from the FDA. Can we have those questions from the FDA put up?

The first question is, "Based on the information provided, please discuss the description -- wait. I'm on the wrong thing. Hold on. I'm sorry. Let's try that.

"Please discuss whether individual

endpoints, composite endpoints, or a combination of both should be. used to evaluate the safety and effectiveness of the Amplatzer AS0 device." I jumped ahead in anxiety to get through this to this afternoon's questions. That's the real question up there.

Any comments from the panel on this? Please discuss whether individual endpoints, composite endpoints, or a combination of both should be used to evaluate safety and effectiveness.

Is there something -- maybe Dr. Wittes. You looked like you're'posed to give us an answer here.

DR. LASKEY: Isn't this the domain of study design? I mean, this is a little late to be discussing this, choice of endpoints.

MR. DILLARD: Jim Dillard. We're in a little bit of a quandary here, I guess, because it is important obviously for study design to sort of prethink about what it is that we're going to use as the analysis tools in order to sort of define the hypotheses going in.

In this case we had some predetermined

individual endpoints. We also had some thinking and some input from clinicians saying that perhaps a composite might be an appropriate way to look at this data and interpret it also.

I think at this point what we are really trying to get at is since we have both, it's important to understand what perhaps is going to be the best way -- if you recommend this be approved, the best way to actually portray the data in the labeling, for example, and how to best get this information to patients. I think it's important for analysis and it's also important for later on how we portray the data.

DR. TRACY: My personal observation on differentiating between success of Point A versus Point B is that it's led to confusion here and that the ultimate question is did it work or did it not work? Was the patient better off or not better off having had the procedure done in either way?

I think to that and the final endpoint whether it's a six-month or 12-month endpoint would probably be adequate but I think you have to know

early on whether acutely the procedure has been considered successful.

From an analysis standpoint I think it makes it a little bit difficult to deal with these various endpoints. From a procedural standpoint and understanding what's happening to the patient, those points have to be analyzed as you're going along. I think it's the difference between a procedural need to know versus how do you deal with the data. I think deal with the data has'a final outcome is probably reasonable.

Dr. Williams.

DR. WILLIAMS: Could I -- my point in saying that the 12-month endpoint is more important is to remember that for the usual indications these are asymptomatic patients. The procedure is done to prevent long-term complications.

The likelihood that a complication will result from a shunt that remains present at six months is negligible with the exception of perhaps cryptogenic stroke or right-to-left embolus.

But for the indications of closure for left-

to-right shunt, I think it's meaningless if there is even a moderate shunt at six months that is closed at 12 months. That's why I think the longer term is the only important issue.

DR. TRACY: Does that get to the issues the FDA was raising?

MR. DILLARD: Almost. Maybe I could ask for one clarification for what Dr. Williams just said. Do you think 12 months and presence or absence of shunt would be the most important way to look at, or do you think the fact major complications embolization, technical failure, etc., also is important to include in that analysis?

DR. WILLIAMS: In my mind I think it's important to note both separately because of the issue that many parents or patients would happily take the risk of failure as long as there are no complications and so to keep those two issues separate.

I think, in fact, there are issues relative to the age group problem that are separate for efficacy and for safety. That is, I really do believe that the older population is at higher risk for

complications despite the pericardial effusion issue because I think they are also at risk for post-pericardiotomy syndrome.

Whereas it may be true that they are given the anatomic variation in the younger group, they are a little bit more at risk for residual shunt or the decision not to deploy the device once they get into the cath lab because of anatomy that was not expected.

DR. WHITE: Could I just way one thing? I think the best number for me is not given here and that is that the 12-month composite success number is a very good number with the caveat that you allow the successes to occur.

What I'm saying is that they were originally asked to count an immediate failure or shunt as a failure. At 12 months if it closed they weren't allowed to add that as a success. I think if I had to give a family a single number, it would be the composite success with the ability to convert an initial failure to a late success.

DR. TRACY: Which I think, parenthetically speaking, gets to the very critical nature of the

patient education that they understand that what you see today is not necessarily what you see in a year.

lb. The sponsor is seeking approval for a device sizes from 4 mm to 38 mm. Approximately 89 percent of devices implanted in the pivotal ASD study were between 10 mm and 28 mm. Is there sufficient data to support approval of the entire range of devices from 4 to 48 mm or a specific range of device sizes?

I think my read on the comments that have been made, and perhaps Dr. Crittenden will correct me, is that there have-been use of the various sizes of devices from minimum to maximum. Perhaps not in equal numbers but that restricting the size ranges to those where they were more used would unintentionally or adversely restrict to the devices available to a variety of patient populations.

DR. CRITTENDEN: I agree. I think there's enough data from what we've heard from the sponsor's presentation that we probably ought to approve all the sizes that they've asked for in the application.

DR. WHITE: We might consider later on a

post-marketing follow-up of those sizes that were less used.

DR. TRACY: Dr. Wittes is grimacing.

DR. WITTES: I'm bothered by this. Maybe I need some help here. This 12-month composite in this gradient that we're seeing with size, you really think that once the data are analyzed correctly with the failures that became successes, once those are back in those numbers will look better?

Because the way it looks to me that is not convincing to me when I look at these data that they shouldn't have surgery if you're going to have to have one of these big devices. That's really what I'm asking.

DR. TRACY: Can you point us to the page that you're on?

DR. WITTES: Yes. It's page 40, the yellow 1.0. I recognize that these are not going to be really the final numbers and that's part of why it's hard to interpret.

DR. WILLIAMS: I think that's part of the territory of having a large device. You have more

opportunity for having the media shunt, residual shunt. That is the point of endothelialization. If that really occurs as those margins are secured and also the central part of that device is closed off. Those shunts go away.

That's why I think it is so important to only include the late data because those large devices have to leak more as best as I can understand. I think it's part of the territory of closing the large defects. The important issue is ultimately does it close.

DR. WHITE: But you're saying you think those numbers will get better?

DR. WILLIAMS: Well, they did.

DR. WITTES: How do we know that they did?

DR. WHITE: It think they told us that -- I don't want to speak for the company. I thought they said that at six months they had them all closed.

Do you want to reiterate what you said about the six-month follow-up? You had six-month follow-up on almost all your patients and how many patients at six months did not have a closed shunt. It was a very

few number.

DR. WITTES: Well, do you have table 32 with the correct numbers? Maybe that would just do it. Table 32 corrected for the real status at 12 months.

DR. WHITE: You had a slide up of your failures. Can you put that overhead back up?

MR. LOCK: Jodi, can you grab --

DR. WHITE:. You're not going to be able to answer that question because they counted those initial composite successes as failures and weren't allowed to convert them. I don't think they know how many to shift.

DR. TRACY: Yes.

DR. LARNTZ: This is Kinley Larntz. We do know that if you do eliminate the procedural shunts the composite success rate goes up to 91.7 percent from 85. About 6 percent of those cases were procedural shunts and those went away.

Now, the main aspect -- I apologize if I'm going over territory I've covered before. The main reason the composite does not have the size effect is that there are technical failures in that group so

there is an inability to -- on occasion the device doesn't get placed because of rim or something like that.

That is the primary thing that is going on with respect to age -- excuse me -- with respect to size. There does appear to be -- it is more difficult to make sure that you've got a device placed properly. Some of those were pulled out and not included. Technical failure means the device didn't get placed. There is a higher rate of that and that's where the composite -- that's the association of composite with size.

DR. WILLIAMS: Well, I'm just a country cardiologist but it seems like if there's more rim, there's more opportunity for there to be a leak between the rim and the atria1 septum. I guess my question would be of those devices that were placed that continued to have a shunt, at 12 months what were those sizes?

MR. LOCK: Jodi, could you put up slide No. 4, please, on the overhead?

This is Ken Lock. Again, I apologize for

the darkness of the slide. You can look over at the primary efficacy column, the third from the right. You can see that the five failures at one year, there was one size 15, one at 16, one at 19, one at 20, and one at 24. Those were the failures.

DR. TRACY: Okay. Thank you.

Dr. Hopkins.

DR. HOPKINS: Yes. In discussion with the other panel members, I'm actually in agreement with both panel members. I think Dr. Williams is exactly right, that the outcome that exist at 12 months or even beyond is really the important outcome. For that reason those so-called early trivial failures really are not failures and shouldn't be so counted.

On the other hand, when you're talking about recommending to adult patients with a large ASD that closure of the ASD should be accomplished to prevent or reduce your risk of bacterial endocarditis and reduce your risk of paradoxical emboli, the absolute closure rate at some point in time does become important. I think you can look at it either way but it's really that sort of 12-month and beyond data.

I'm sort of presaging the last question because I think there are questions that have bedeviled this panel now at two complete different sessions having to do with size and also with age that really still are not completely answered. I share your concern about the younger age group in terms of the comparative data.

I also agree with you in terms of the olders that a larger defect is clearly going to have larger residual defects and it's really the issue of whether they are actually completely closed at 12 months. Both the composite and the specific are important and over time.

DR. TRACY: Okay. So I think that gives us lots of comments pertaining to both la and lb. We'll move on to question 1c.

Based on the data provided on ASD patients and the suggested analysis of the data from question 1a, please discuss whether these data provide reasonable assurance of safety and effectiveness.

I will look around the table and see if anybody is wagging their head no. I think that there

are data to support the safety and effectiveness of this device and that it's just a little bit difficult analyzing what time should you ask the effectiveness question.

DR. LASKEY: Well, with some qualification because at the extremes here we don't have a lot of data points. I mean, there's a lot clustered in the middle but this is just what we've just been talking about for the last hour really, the extremes of size and age. There's not a lot of information so I don't necessarily agree with that, particularly with the efficacy.

DR. HOPKINS: I would separate the two. I think there is adequate data for safety but I'm still concerned. I would like to see the actual analysis in terms of efficacy for the lower age group and for the larger size group. I haven't seen that analysis here.

DR. TRACY: I think those would be -- the one analysis in terms of the younger age group should be doable from the data that is already available. In terms of the effectiveness, if we are saying that effectiveness at 12 months is more important, then it

seems like. something that would have to be followed over time so with those additional comments.

Question 2. To support the fenestrated Fontan indication, the sponsor has submitted data from a single-arm registry with 48 patients. Based on the data provided on fenestrated Fontan patients and the suggested analysis of the data from Question la, please discuss whether these data provide reasonable assurance of safety and effectiveness.

DR. McDANIEL: I was going to say there is safety data there. Efficacy again depends on how you define applications and closing of Fontan. They got the shunts down to 2 mm or less.

DR. HOPKINS: I think this is one where the comparison with surgery does become very critical because the risks of surgery, the difficulty of surgery is not at all the same question as the routine ASD. That's why I think this is a much simpler question.

DR. WILLIAMS: I also think there's so many confounding variables in this population. It would be impossible to ever decide that perfectly.

DR. TRACY: Yes, Mr. Dillard.

MR. DILLARD: Yes. Jim Dillard. Maybe just one clarifying question. This is an issue we struggle with considerably and I think we've been beat up as the agency on both sides fairly well so I would love to get any comments from this panel.

If we have a completed study, a study that hopefully gathers patients over the range that would be appropriate clinically to take a look at a device, and yet we know we will never generally have enough patients no matter how many subgroups you wish to break it up into, one of the things we do as the agency is we will do exploratory analyses certainly on subgroups to look to see if there is anything particularly odd about those subgroups.

Generally as we try to break up those subgroups, and if we want to change an indication based on some of those subgroup analyses or only approve the device for some of the subgroups if we've got an overall successful clinical trial, I think it's problematic from a number of different perspectives, maybe most of which I think we get different comments

from the statistician certainly on both sides pro and con.

I think it would be probably an injustice to clinical trials if we started doing the exploratory analyses on a regular basis and then trying to make that the justification or the basis for approval of the subgroups only if we had an overall successful clinical trial.

I would love to get any comments from the panel about if we did some of these exploratory analyses, what is it that you think we ought to look for and what do you think would be important then. I heard certainly size and age but they are going to be awfully small numbers.

DR. LASKEY: Jim, are you talking about both issues or are you just talking about the fenestrated Fontan right now?

MR. DILLARD: Well, I think it's come up in both of them. I know it's been precipitated based on the Fontan question because we're there but I think you certainly had some comments on both of them whether it be the ASD or the Fontan patient

population.

DR. WITTES: Well, may I just ask you -- the Fontan I couldn't address because I didn't see what the comparison was. I didn't know how to even read it. It seems to me there is a really big difference between data dredging in the clinical trial and data dredging in a poorly controlled study.

It seems to me in the first you don't want to and in the second you really do because you don't have -- I think there has to be aggressive analysis. You want to make sure that there's nothing in the artifacts of the control group that is making things look better than they should.

It may be in this particular case that because of the way of doing analysis you are, in fact, being very conservative with respect to the surgery. I don't think -- other statisticians may disagree with me but I think one has to do exploratory analysis when one doesn't have randomization.

DR. HOPKINS: I would agree. I don't know if you had arrived when I pointed out I think that some of the negative outcomes of the surgery group are

arguable. Yet, I agree with Dr. Williams that the device has been unfairly treated in terms of the 12-month outcome.

I think there are, in fact, confounding variables on both. When we get to the last question I think there are going to be some recommendations from this panel.

MR. DILLARD: Great. Thank you.

DR. TRACY: Question 3: A summary of the physician training program has been provided in Section 5 of the Panel Package. 3a. Please discuss any improvements that could be made to the training program.

Any comments from the panel?

DR. LASKEY: Case selection should be the first 10 items in the training program.

DR. TRACY : Probably case selection and being certain that the operator understands the definition of endpoints and what they are looking for as the outcome of the procedure as well as all the technical aspects.

Any other comments on that?

Question 3b. More than one device was placed in 10 ASD patients. Please discuss training issues regarding the placement of multiple devices in a single patient.

I would think that would be not the first thing that somebody would take on. That and the larger sizes. You had mentioned that a proctor might be present for something like that. I think those very complex things would be best handled either with a very experienced proctor or in the proctor's hands while the operator is gaining experience.

Other comments?

Moving onto product labeling. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations per treatment with this device. That is in Section 3 if people want to flip to that.

We did have some comment early in the discussion. That goes to contraindications.

DR. LASKEY: Well, we have some assurance that first paragraph will be modified to eliminate the paradoxical embolus or PFO population.

DR. TRACY: The first paragraph in INDICATIONS FOR USE?

DR. LASKEY: Yes, towards the end of that paragraph. That's refers to that population. So these patients must have hemodynamic evidence of volume overload.

DR. TRACY: Okay. 4b.

DR. HOPKINS: Wait a minute. Can I ask a question? Are you suggesting that a patient who has had a paradoxical embolus through a small defect but does not have RVH would not be a candidate for closure? Did I hear you right or did I mishear you?

DR. LASKEY: No. I didn't say that at all but I would answer your question there's nothing in this Panel Pack that would support anything along those lines either with regards to safety or efficacy.

DR. TRACY: So are you suggesting just a revision in the wording to eliminate paradoxical embolism? What exactly would you suggest there?

DR. LASKEY: Well, I -thought we had the assurance of the company that they were going to somehow modify this language so that it becomes clear

that the INDICATIONS FOR USE of this device are patients with a secundum ASD with evidence of right ventricular volume overload and/or clinical symptoms.

DR. TRACY : So essentially the patient population as reflected in the patient includes --

DR. LASKEY: Yes. I mean, that's both a question as well as a reiteration of my understanding. I personally think you ought to avoid the paradoxical embolism population.

DR. TRACY: Dr. Williams.

DR. WILLIAMS: I would prefer that we say that the indications in that case have not been established rather than it's contraindication because we don't know it's a contraindication. We just don't have the data in that subset to support it.

DR. LASKEY: Correct.

DR. HOPKINS: I'd agree with that.

DR. TRACY : That could be specifically mentioned that 'there are no data dealing with that specific group.

DR. SKORTON: Another possibility would just be to cross it off. Just take it of period because

the first part of the indication, the first four or five lines, is what the whole PMA is about. The part after "or" there is no data on so I would be in favor os just killing everything after the parenthesis ends.

DR. TRACY: I guess that's one option but then that might leave the physician open to the question should I or shouldn't I and what are the data that support or were any of those patients included in this study.

I think that in the indication I would agree that just lopping it off after the or part would be appropriate but in the specific description of the patient population there should be a statement that no patients were included who specifically had X, Y, Z.

DR. WHITE: I guess, Warren, just to go back to your question, if you would send a patient for surgical correction of an ASD because they had an paradoxical embolus, and if the endpoint that you wished to achieve is closure of the ASD, then I think what the data says in front of us is that the ASD is closed.

The question about whether or not you can

stop further paradoxical embolus is what's not addressed. I think we need to be careful about how the clinician who is faced with this choice of closing an ASD how do we help him? How do we help her or guide that person's decision?

I mean, we're not looking at efficacy of paradoxical embolus but it looks to me like this device closes ASDs. So is it not appropriate then to leave it in the language or some in some other way?

DR. TRACY: I think -- my instincts would tell me to take it out since it's not included in the population. Plus there are whole issues of anti-coagulation that are not addressed if somebody has had a paradoxic embolus. We don't have any data that would say what to do with them with a device that may take a year or two to completely close an ASD. We don't know what to do with that patient given any of the data that is here in this application. I think rather than specifically mentioning them here where they were not included in the initial data, I think we should just take it off and then comment.

DR. WHITE: I think there were some patients

included enrolled in the trial for this indication. Was there not?

DR. TRACY: Three.

DR. WHITE: A few.

DR. HOPKINS: Why wouldn't you just say indications have not been established for these two specifically because I think it is going to come up.

DR. TRACY: It will. Somehow it has to be addressed either 'here or following the table. But I don't think we have established this as an indication for this device based on three patients out of the entire study.

DR. HOPKINS: So just say that.

DR. TRACY : It's not a contraindication though either. You can work out where you want to put that.

DR. SKORTON: Could we talk about this a little tiny bit more? I think it's more than just a PFO. The other condition in which a person could have clinical symptoms of paradoxical embolus and the minimal shunt is someone with early Eisenmenger's physiology which also wasn't studied.

Three patients out of this to me doesn't make indication. I'know you're not arguing for it to say it is an indication. I think it's more than just PFO. I think the indication that is strongly supported is for the common garden variety secundum ASD with a big shunt. I don't have any qualms about that whatsoever.

PFOs and early Eisenmengers, I just don't know what to make of it. I mean, you could say indications haven't been established. That's fine with me. I just wouldn't want to see that part left in the indication section. That's my only point.

DR. TRACY: I think that's a good point. I think that is pretty clear. It should be removed from the indication.

Okay. 4b. Please comment on the contraindication section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

I think we were struggling to get a slightly tighter definition of any patient whose condition

would cause the patient to be a poor candidate for cardiac catheterization. Maybe something slightly more specific. Size is obviously important and that is in your statement there. What other conditions make the patient a poor candidate?

DR. SKORTON: I'm sorry if I missed it but I thought in the discussion with the clinicians it was suggested that transesophageal echo was a very important part of this so there might be a contraindication if the person is not a candidate for transesophageal echo because of esophageal disease.

DR. WHITE: But if you can do intracardiac echo I think you can compensate for that.

DR. TRACY: That's right. ICE might take the place of TEE. Would you still feel that way if you could gain the same data by ICE?

DR. SKORTON: I guess I would personally feel okay about it but we're talking about labeling now and not how I feel. I think that intracardiac echo is not a universally applied technique. This is going to be universally marketable if we take a certain action.

I'm okay with that if we put some words in to that effect. Relative contraindication if you can't do TEE. If ICE is available, one could consider that. That means if there is a medical center where they don't do ICE, which I'm betting is most med centers, and the patient is not a candidate for transesophageal echo, it might be a contraindication or relative contraindication.

DR. LASKEY: Is Doppler a part of ICE now?

DR. HIJAZI: Yes.

DR. WILLIAMS: But it would make sense for those patients who have esophageal abnormalities be done in a high resource center that had the availability of ICE.

DR. TRACY: Okay. So adding some wordage in there about the use of TEE and relative or absolute contraindications that might exist for that. And some other plan would have to be in place to deal with those patients.

Does anybody want to raise the nickel allergy again? I don't know that that is a contraindication or whether that should be somewhere

mentioned maybe as a warning or something, but I think it should be raised since nitinol may not mean anything to other people and the patient has to understand that there is nickel in there.

4c. then. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

DR. WHITE: I think that under 4.2 we need the specific wording about onsite surgery needs to be listed.

DR. TRACY: 4.2, is physicians must be prepared to deal with urgent situations which require removal of embolus devices that result in critical hemodynamic compromise. Yes, that should have some wordage about having surgical backup available.

Any other comments on warnings/precautions? I think there should be some wording in there about this does not supplant the need for Coumadin if there is another contraindication. That should be in there. Or another indication for the use of Coumadin. That should be in there somewhere.

4d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

DR. WHITE: Well, I read through these as an operator who does these and they are tedious. I can't criticize them. You do need the proctor with you. These do not supplant the need for someone with experience with the device. You can't open a package and do this. I wouldn't criticize what they've written. I think they've done about as well as you can do but that just doesn't suffice alone.

DR. TRACY: This very clearly is a procedure that needs proctoring.

4e. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

If we are including the patient package, I think there are some issues there. The principle is good but the language needs tightening up and there's some actual physiologic things that were incorrectly

stated in there.

Any other comments?

DR. WITTES: Can I add something? I would still like to add something to Table 5 because the person who reads this is going to only notice the age difference in one demographic table and this is going to be hidden away. It seems to me that one could take another panel of Table 5, just mimic it, and stick the less than 20 or some age group that you really have reasonable comparisons to.

DR. TRACY: That may come up again here in our next question.

Post-market evaluation. The Panel Package includes the available one-year data for the Amplatzer device. Long-term adverse effects that may be associated with device implantation include late thrombosis, etc., and arrhythmias.

5. Based on the clinical data provided in the PMA, do you believe that additional follow-up data or post-market studies are necessary to evaluate the chronic effects of the implantation of the Amplatzer device. If so, how long should patients be followed

and what endpoints and adverse events should be measured?

I think there are a number of comments. Maybe, Dr. Wittes, you can restate what you just said in terms of looking --

DR. WITTES: But what I had to say was actually different from this. This is more how should you follow individual patients and what's happening in long term.

Mine was just for Table 5 which shows the overall results including the group. I'm still worried about the. group that doesn't have an age comparison. All I want is to make sure that the comparison is there.

DR. TRACY: Okay. Would it be worthwhile asking for follow-up on -- 1 guess we can't ask for more surgical data on older population. Is there anything we can do to improve the patient population that we're looking at here? Increase the population? Do we need to?

DR. HOPKINS: I think this is an important part of the panel's recommendations. I think that

safety and relative efficacy has been shown here. I think the concern is that at the two ends of the spectrum we're still not absolutely sure about efficacy.

Therefore, I think the panel should recommend that there be designed at least a registry type of approach. If not looking at every patient who receives one of these devices, at least looking at those subgroup of patients who fall into those two areas, the large defect and the younger patients and the long-term residual shunt patients, as to what the long-term efficacy of this device is because that's fundamentally the question here.

The fact is it has been shown they are safe, that you can stick these things in and not hurt a lot of people. The question is really should this be the procedure of choice.

Unfortunately it is a long-term question but it is a question that has not been answered yet. I would recommend to the panel that we seriously consider requiring at the minimum a registry type of approach to asking that question over the relative

long term about those two groups.

DR. TRACY: I guess the question is how long is long?

DR. HOPKINS: Well, when the ASD is completely closed at age three, the patient has a normal heart. It's being proposed that closing the ASD returns the patient to a normal life expectancy.

You could argue they should be followed for life. I'm not necessarily proposing that, but I am proposing that I think that the large defects that are residual, that probably somewhere in the range of five years for the younger patients and somewhere in the range of five to 10 years, that a registry data and follow-up should be required so we can answer that question.

Dr. Williams.

DR. WILLIAMS: I agree with what Dr. Hopkins has said in terms of efficacy. I also maybe raise the question reacted to by my other colleagues in terms of safety for the largest devices which is a rather inflexible structure.

There have been some very sparse and non-

peer reviewed abstracts that have suggested for very large atria1 devices there have been some interference with shortening of the long axis of the ventricle in systole which may have some affects on ventricular function.

You would also wonder because if its location the very largest defects whether there could be some distortion of either the AV valve embolism and the function in that area.

Or perhaps some distortion of the aortic root with aortic insufficiency and if there shouldn't be some post-market surveillance with the very largest defects for both AV valve and posterior semilunar valve insufficiency as well as ventricular function. I really don't know how long. Maybe 10 years or so. Maybe Dr. Zahka has an idea about this.

DR. ZAHKA: I've actually struggled a bit eve this morning back and forth about what I think should be the long-term follow-up for these devices. Ideally it would be wonderful to have a lo-year follow-up, five-year follow-up where we had some kind of control group as well.

Since I think there are going to be a proportion of surgical patients who have ASD closure who are going to have arrhythmias, I don't know what I would do as a panel member 10 years from now, hopefully in my retirement, where we sat here and said, "Oh, my God. There are arrthymias 10 years out," because we don't have the control group.

Yet, I would wonder if we're going to start seeing aortic regurgitation or AV valve regurgitation. My sense is we're going to see that by a year. Are we, in fact, accomplishing anything by the five or 10-year follow-up? I assume there. is going to be some kind of like a pacemaker registry at the company of these patients.

If the case reports and the medical literature do begin to suggest that there is something going on, I would hope that we would then be able to in a very systematic say recall patients for a prospective evaluation at that time when we know what we're looking for and be able to collect the data in a very logical and effective way.

DR. WILLIAMS: I'm persuaded by the

arguments of my colleague but because of the stockmarket I will probably still be working.

DR. SKORTON: I have a compromise to suggest. I'm still a little bit uncomfortable with some of the subgroups, and yet I think 10 years is a very long time. A lot of things change in 10 years. I better be retired in 10 years.

Also, we need to help the FDA and the sponsor by giving some discrete endpoints and things to look at. Just as a strawman, I'm going to suggest that we recommend a five-year post-market surveillance of the groups implanted with devices larger than 28, smaller than 10, those with residual shunts, and those implanted under age 10 years.

And at the endpoints we look for our just thrombi and endocarditis and general cardiac function on echo, that we don't do the arrhythmias because they are very hard to interpret.

Those might not be the exact right ones but something like that where we give them a discrete number of things to look for and those will be the things based on which the FDA would call us back to

talk about them later.

DR. WHITE: As an adult cardiologist could I suggest that we might include the paradoxical emboli patients and follow them as a post-marketing surveillance. This is a small population of patients that are not likely to be prospectively studied. IT's not likely that we are going to see data on ASDs with paradoxical emboli to above.

This is an opportunity to collect that data in a post-market environment which would be fairly disciplined. The device is performed in a small population of these patients.

I understand the difficulty in feeling comfortable about the prevention of the paradoxical emboli but I'm not uncomfortable about the ability to close the ASD. That's why I feel like the glass is more half empty than half full about this.

DR. TRACY : That would suggest that the structure or the registry would include data for the clinical indication and that would be one of the questions that would be asked.

Mr. Morton.

MR. MORTON: Could I make a couple of comments? The agency recently sponsored a workshop on post-market studies and surveillance and it concerns me that we're using the term registry because registry I know from experience with other devices they are awkward.

They are difficult to deal with. You get a lot of information that is not necessarily the information that you want. It's not necessarily information that is going to answer the questions that you're asking here. I would suggest that really you're not looking at a registry. In your recommendation is was not a registry. It was not.

I would also ask that we ask the sponsor actually is there information in both their cohort and in their continued access study. That seemed to be quite a few patients. Could there be data there that is going to answer these questions without moving into a true post-market study which would be extremely difficult to manage?

DR. TRACY: Those are very good points.

DR. HOPKINS: I stand corrected on the

registry. I actually think, Dr. Skorton, your recommendation is very close to being on point. At the five-year you might identify one or two issues that need to be followed another five years.

I think we have evidence that certainly with valve patients we've significantly altered their national history and they really need to be followed for a long time before we really sort out what the best options are. I think the case is going to be similar here. I-think it's a good on-point.

DR. TRACY: Dr. Zahka.

DR. ZAHKA: I was just wondering if there was a one in a thousand or one in 500 risk of a late thrombus and/or endocarditis, would that change our recommendations today if we knew that information today? Or one in a hundred with endocarditis or late thrombus.

DR. SKORTON: That's really a tough question to answer but I think the answer is it's not just a matter of what-we would do. It's a matter of what the materials in the device might change. The way it's put in might change. The anti-coagulation you give

might change. There are so many moving parts.

Plus the companies aren't going to stand still while this is going on. They are going to develop better materials, different wires, different polyester. I think it's a moving target.

I think that your point is well taken about not having a widely open registry. I think a tightly focused series of studies and follow-up will make us feel better and will help move the field along.

It won't be too intrusive on the company's time or on the clinical' investigators. I think we make our best guess now as to the things we want to follow and hopefully we don't find anything.

DR. TRACY : That covers the written questions by the FDA. Does the FDA have any additional questions or comments at this time?

MR. DILLARD: No. That's it from FDA. Thank you.

'DR. TRACY: Okay. Does the sponsor have any additional comments? Okay. Then at this point I would like to give time for an open public hearing. Is there anyone in the audience who wishes to address

the panel on this topic before we take our vote? Okay. Then we will close the open public hearing.

MS. MOYNAHAN: I'd like to read through the options for the vote.

The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the FDA to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by the safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use as conditions of use when labeled will provide

clinically significant results.

Your recommendation options for the vote are as' follows:

(1) Approval if there are no conditions attached.

(2) Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting all of the conditions should be discussed by the panel.

(3) Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. TRACY: I'd like to ask for a motion at

this time regarding the approvability of this device.

Dr. Williams, as the lead reviewer, you are certainly welcome to make that motion.

DR. WILLIAMS: I move approval of the use of the Amplatzer Septal Occluder device in patients with ASD in the secundum position and patients requiring closure of the fenestration following a fenestrated Fontan procedure.

DR. TRACY : Are there any conditions you would like to place on the approval? Does any panel member feel that any conditions should be placed on this?

DR. LASKEY: I do. I think we've discussed that. I think the conditions to be applied pertain to post-marketing surveillance of some high risks of groups which I guess we can discuss openly here.

She recommendedapprovalwithoutconditions. There is no second part so the first thing is do we have a motion.

MS. MOYNAHAN: Is that what you were suggesting. as approval without any conditions attached?

DR. WILLIAMS: No. Actually I had thought we could then say if there was an amendment with conditions. I move for approval with conditions of post-market surveillance.

DR. TRACY: Then if we could delineate what those conditions are, we'll discuss and vote on each of the conditions before we vote on the approval. So we have one condition is that there must be some type of surveillance put in place to look at the patients at the extremes, the large size and the younger ages, and following those devices over time the exact mechanism of that surveillance is not determined. There may be data available within that total population which can give some of that information but there likely will need to be some ongoing surveillance of the device. Does that state what the panel intends?

MS. MOYNAHAN: I think we should vote on each one separately, each condition.

DR. TRACY: Okay. All those in favor --

DR. HOPKINS: Point of process. How specific do you want us to be on these conditions?

MS. MOYNAHAN: You can refer to your earlier discussion and say as we discussed earlier. For example, with labeling or the post-market surveillance.

DR. HOPKINS: Then I would like your motion really, or the amendment to your motion, that it be really to suggest Dr. Skorton's recommendation for the post-market surveillance studies.

MR. DILLARD: Jim Dillard. Just a real quick recap of process. I think you've got a motion on the table for approvable with conditions that was seconded by Dr. Skorton. Now we're at condition No. 1 which is a post-market surveillance effort.

I think you can have any discussion that you want associated with that particular condition and then you can go ahead and vote on each particular condition and then at the end on the entire motion if that helps.

DR. TRACY: so the condition -- the condition is that we have post-market surveillance. Referring back to the earlier conversations, Dr. Skorton laid out some pretty, I think, reasonable and